

# Zolmitriptan and human aggression: interaction with alcohol

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## Abstract

**Rationale** The serotonin  $1_{B/D}$  (5-HT $1_{B/D}$ ) receptor has shown potential as a target for decreasing aggression. The 5-HT $1_{B/D}$  agonist zolmitriptan's ability to reduce aggressive behavior in humans and its interaction with the well-known aggression-enhancing drug alcohol were examined.

**Objectives** Our objective was to investigate zolmitriptan's potential to modify human aggression in a laboratory paradigm across a range of alcohol doses. Alcohol has been consistently associated with aggression and violence, thus we hoped to expand current understanding of alcohol's role in aggressive behavior via manipulation of the serotonin (5-HT) system.

**Methods** Eleven social drinkers, seven male, were recruited to participate in a research study lasting 3–4 weeks. Aggression was measured using the point-subtraction aggression paradigm (PSAP), a laboratory model widely used in human aggression studies. Subjects were administered 5-mg zolmitriptan and placebo capsules along with alcohol doses of 0.0, 0.4 and 0.8 g/kg in a within-subject, counterbalanced dosing design. Data were analyzed as the ratio of aggressive/monetary-earning responses, to account for possible changes in overall motor function due to alcohol.

**Results** There was a significant alcohol by zolmitriptan interaction on the aggressive/monetary response ratio.

Specifically, compared to placebo, zolmitriptan decreased the aggressive/monetary ratio at the 0.4- and 0.8-g/kg alcohol doses.

**Conclusions** A 5-mg dose of zolmitriptan effectively reduced alcohol-related aggression in an acute dosing protocol, demonstrating an interaction of 5-HT and alcohol in human aggressive behavior.

**Keywords** Serotonin · 5-HT $1_{B/D}$  receptors · Agonist · Human behavior · PSAP

## Introduction

Serotonin (5-HT) has a longstanding relationship with aggression and violence that has been demonstrated across gender and species (Westergaard et al. 1999; Miczek et al. 2002). For example, cerebrospinal fluid (CSF) levels of 5-hydroxy-indolacetic acid (5-HIAA), a 5-HT metabolite, have been negatively correlated with lifetime history of aggression in an inpatient population who had demonstrated past antisocial behavior (Brown et al. 1979). Although not all studies have found a negative correlation (Moller et al. 1996), a meta-analysis found a significant mean effect size of  $-0.45$  for increased aggressive behavior as 5-HIAA decreases (Moore et al. 2002). Further, individuals with conduct disorder, a personality disorder typified by extreme aggression, have lower 5-HT profiles than healthy controls (Cappadocia et al. 2009). In consequence, the 5-HT system has shown potential as a target for the therapeutic treatment of aggression (Siever 2008).

One established laboratory assessment for human aggression, the point-subtraction aggression paradigm (PSAP), is a free-operant measure of aggressive behavior that allows subjects to subtract money (represented on a

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computer screen), later to be exchanged for real money, from a (non-existent) confederate in a computer task (Cherek 1992). Subjects are provoked throughout the session by subtractions from their counter (attributed to the confederate) and can freely choose the aggressive option throughout the course of the task, but they are never forced to use it. The primary measure of interest is the frequency with which the individual uses the aggressive response option. Thus, the PSAP indexes the frequency of aggressive behavior. By comparison, another common task, the Taylor aggression procedure (or TAP), measures the intensity of aggressive behavior (McCloskey and Berman 2003; Taylor et al. 1976; Parrott and Giacola 2007). Previous studies in subjects with histories of frequent aggressive behavior, criminal violence and disorders associated with aggression (substance abuse, antisocial personality and borderline personality disorders) have documented the external validity of the PSAP (Cherek et al. 1997, 1999; Gerra et al. 2004; Golomb et al. 2007; Moeller et al. 1998).

The PSAP has also established sensitivity to 5-HT manipulation, as one study demonstrated that acutely lowering serotonin levels via tryptophan depletion can increase aggressive responding (Moeller et al. 1996). When tryptophan depletion accompanied alcohol administration, the effects on aggression were additive and aggressive responding increased to higher levels than following alcohol administration or tryptophan depletion alone (Dougherty et al. 1999). Aggressive responding on the PSAP was also decreased following acute administration of the non-specific 5-HT releasing agents D-fenfluramine and D,L-fenfluramine (Cherek and Lane 1999; Cherek and Lane 2001), and chronic administration of the SSRI paroxetine (Cherek et al. 2002). Notably, paroxetine was also recently found to reduce aggression measured via the Taylor aggression procedure (Berman et al. 2009).

Research supporting a general serotonin deficiency is robust, but receptor function and local 5-HT levels may reveal a more precise mechanism through which 5-HT alters aggression as opposed to systemic changes. For example, Cherek et al. (1999) demonstrated that violent parolees showed less response to a biochemical challenge by the 5-HT receptor type 1<sub>A</sub> (5-HT<sub>1A</sub>) agonist buspirone compared to non-violent parolees, and thus may have lower expression or decreased function of 5-HT<sub>1A</sub> receptors rather than lower levels of 5-HT in general. Research exploring serotonin receptor expression and pharmacologic manipulations targeting specific receptors has pointed to serotonin receptors 1<sub>A,B</sub> and D as well as 2<sub>A, B</sub> and C as targets for modulating aggressive behavior (Miczek et al. 2002).

For over a decade, the 5-HT 1<sub>B</sub> receptor has received attention as a target for anti-aggressive modulation, particularly due to its high concentration in the orbitofrontal cortex (OFC; Boschert et al. 1994), a brain region proposed

to regulate inhibitory control of aggression (New et al. 2004). In mice, the injection of a 5-HT 1<sub>B</sub> agonist into the ventral orbitofrontal cortex (VO PFC) caused reductions in species-typical aggressive behavior without significantly altering non-aggressive behaviors (de Almeida et al. 2006). Notably, a 5-HT 1<sub>B</sub> agonist injected into the VO PFC reduced aggression in socially provoked male mice, demonstrating the potential external validity of 5-HT 1<sub>B</sub> anti-aggressive effects (Centenaro et al. 2008). Studies of human 5-HT<sub>1B</sub> receptors have been inconclusive, as some reports link genetic polymorphisms of the 5-HT<sub>1B</sub> receptor to comorbid alcoholism and ASPD (Lappalainen et al. 1998), while other reports have found no relationship (Huang et al. 1999). In alcohol-dependent men, a single-nucleotide polymorphism (SNP) of the 5-HT<sub>1B</sub> receptor predicted a blunted growth-hormone response to sumatriptan, a 5-HT<sub>1B</sub> agonist, suggesting a relationship between 5-HT<sub>1B</sub> receptor function and the development of alcoholism (Moss et al. 2007). Investigating the role of 5-HT<sub>1B</sub> agonists in humans remains important, especially given their pre-clinical anti-aggressive indications and the evolutionary diversity of aggressive behavior and 5-HT receptor sub-types.

Zolmitriptan, one of numerous triptans, is indicated for migraine relief by acting as an agonist at the 5-HT 1<sub>B/D</sub> receptor, causing intracranial blood vessels to contract and reduce pressure (Peterlin and Rapoport 2007). Second-generation triptans, such as zolmitriptan, appear more selective for cerebral blood vessels than peripheral blood vessels, and thus pose less ischemic risk than first generation triptans such as sumatriptan (Silva et al. 2007). Unlike releasing agents such as D- and D,L-fenfluramine or reuptake inhibitors like paroxetine, zolmitriptan is a direct agonist. Therefore, it represents a potentially unique mechanism of action with regard to effects on aggressive behavior.

Behavioral research using a mouse model demonstrated that zolmitriptan effectively reduced both alcohol-heightened and species-typical aggressive behavior via its actions at the post-synaptic 5-HT 1<sub>B/D</sub> receptor (de Almeida et al. 2001). Although zolmitriptan shows efficacy at targeting 5-HT receptors in the brain and potential to mitigate aggression, to date few studies have examined zolmitriptan's behavioral effects in humans. Indeed, this experiment represents, to our knowledge, the first exploration of any of the triptans to potentially modify human aggression or impulse control.

The  $\gamma$ -amino butyric acid A (GABA-A) receptor also plays an important role in the modulation of aggression (see de Almeida et al. 2005 review). Both epidemiological and experimental data document a well-established relationship between alcohol use, via action at the GABA-A receptor (Harris et al. 2008) and aggression (Bushman 1997; Taylor et al. 1976; Martin and Bryant 2001). Although not all people

who drink become aggressive, those who have a propensity to become aggressive under the influence of alcohol and have been called “aggressive drunks” (Ito et al. 1996); aggressive drunks tend to have higher trait levels of aggression (Giancola et al. 2005). Fifty-four percent of men and forty-three percent of women arrested for any crime reported recent alcohol use, including 51% of men arrested for homicide (Martin and Bryant 2001). Two-thirds of victims who suffered violence by an intimate, such as a spouse or significant other, reported that alcohol was involved (Greenfeld and Henneberg 2001). Clearly, alcohol can play a major role in facilitating human aggressive behavior despite the fact that most individuals do not become aggressive when intoxicated (Hoaken et al. 1998). Relevant to this project, controlled laboratory studies showing the interaction of serotonin (5-HT) and alcohol have been few and have not been conclusive.

Serotonin function, while modulated by alcohol, is affected non-specifically. Ballenger et al. (1979) found that after a minimum of a month of abstinence since their last drink, alcoholics had lower CSF levels of 5-HIAA compared with controls, suggesting that alcohol may interact with the central serotonergic system. Subsequently, as a means of decreasing appetite for alcohol, SSRIs have been used effectively to lower consumption rates in a group of alcoholics (Sellers et al. 1992). In rodents, ethanol administration decreased 5-HT/5-HIAA turnover in the hypothalamus (Akash et al. 2008), suggesting that the release of 5-HT may be down-regulated following ethanol administration. Further, serotonin's affinity for its receptors decreased in some brain regions following ethanol administration (Akash et al. 2008), so ethanol may compromise serotonin function in multiple ways. Alcohol may only decrease 5-HT in alcohol-exposed mice, rather than alcohol-naïve mice, and this may differentially affect aggressive behavior, complicating the relationship between 5-HT, alcohol and aggression (Faccidomo et al. 2008). A study in humans observing the relationship between 5-HT, alcohol and aggression found that while alcohol increased aggression and higher serotonin levels decreased aggression, these effects were independent of one another (McCloskey et al. 2009a). In addition, when a previous study found that tryptophan modulation influenced aggression independently from alcohol's effects on aggression, the authors concluded that lower basal 5-HT may predispose individuals to alcohol-heightened aggression despite the lack of a 5-HT-alcohol interaction (Pihl et al. 1995). As specific interaction effects with alcohol have been inconclusive, the relationship between alcohol intoxication and serotonin function remains a key question for both the etiology and psychopharmacology of aggressive behavior.

Both aggression and alcohol-heightened aggression remain as relevant public health and scientific problems.

This study represents the first exploration in humans of alcohol-heightened aggression with concurrent acute manipulation of the 5-HT  $1_{B/D}$  receptor via zolmitriptan.

## Methods

### Subjects

A total of seven male and four female social drinkers ( $N=11$ ) participated, aged 22 through 40 years ( $M=28.5$ ,  $SD=6.3$ ). Two male subjects met criteria for antisocial personality disorder (ASPD+), one female met for conduct disorder (CD+) but did not meet for ASPD and one male met criteria for ASPD as an adult but did not meet for conduct disorder (ASPD-). One male subject met criteria for borderline personality disorder. No other subjects had personality disorders. Nine were African-American, one Hispanic and one Caucasian. Subjects were all high school graduates, with an average of 14 years of education ( $SD=2.1$ ).

Subjects were recruited via advertisements in local newspapers. Potential subjects who called the laboratory in response to the advertisement were asked a series of questions as an initial, confidential screening. The questions requested general information such as height, weight, drug-use history, education and work history, criminal history, psychiatric history, general medical condition, and for females, whether or not they used oral contraceptives. Volunteers who met initial criteria for the study were then invited to come to the laboratory for more extensive psychiatric and medical interviews. Psychiatric screening used the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV 2000; SCID-I, First et al. 1996) for axis I disorders, and SCID-II NP for axis II disorders.

Prior to screening, volunteers signed an informed consent agreement, indicating their understanding of the study requirements and the risks of zolmitriptan and alcohol administration. All procedures were approved by the University of Texas Health Science Center-Houston's Institutional Review Board, the Committee for the Protection of Human Subjects.

### Subject selection criteria

Research volunteers were included if they had no history of DSM-IV Axis I psychosis or mood disorders (major depressive disorder, bipolar disorder or schizophrenia), no current or past history of chronic medical problems (noting particularly the absence of pulmonary, cardiovascular, renal and liver diseases, diabetes and seizures), no current use of CNS-active medications (to prevent drug interactions) and no history of brain injury or major head trauma with loss of

consciousness greater than 15 min. Volunteers also had no history of current or past substance dependence (including alcohol), in order to rule out confounds of unique neurological or behavior histories associated with chronic drug use. Two male subjects met criteria for past alcohol abuse; one of whom also met criteria for ASPD. Only individuals with a body mass index (BMI) below 30 were selected in order to avoid problems with drug distribution and elimination in obese individuals, and to decrease variability in absolute alcohol volume administered across subjects.

All subjects reported regular alcohol use 2–6 times per week, but not more than 12 drinks per week, and drinks were not consumed during a single episode (i.e. not binge drinkers); these criteria constituted our definition for social drinking. Drug and alcohol use histories were obtained from all subjects. Participants were also excluded following any evidence of adverse reactions to 5-HT based drugs, cardiovascular complications indicated by the results of an electrocardiogram (four recruits), substantially increased blood pressure following administration of zolmitriptan (one recruit) or adverse reactions to the 0.8-g/kg alcohol dose (one recruit). Summing the subjects who dropped out and all excluded subjects, a total of 15 subjects signed the consent form but did not complete the study.

#### Extraneous drug use

Extraneous drug use was monitored by obtaining urine and expired-air samples each morning. Urine samples were subjected to complete drug screen analysis, performed using the Enzyme Multiple Immunoassay Technique Drug Abuse Urine Assay (EMIT d.a.u., Sylva Corp., Palo Alto, CA). Detection of illicit drugs (cocaine, opiates, benzodiazepines, stimulants or marijuana) in urine samples resulted in participants being released for the day and asked to return once a drug-negative sample could be provided (one incident). Two consecutive positive drug samples resulted in the subject's removal from the study (0 incidents). Alcohol consumption was monitored via an Alcosensor III and obtained each morning to ensure that subjects began the day with no alcohol in their system. Use of any psychoactive medication was prohibited during participation. Smokers were excluded if they consumed more than five cigarettes per day to prevent complications from either nicotine interaction or withdrawal. Participants were not allowed to drink caffeine or smoke cigarettes between 8a.m. and 3:30p.m.

#### Considerations for female subjects

Previous studies in the UTHSC-Houston laboratory have found no differences between male and female subjects in

baseline aggressive behavior (Allen et al. 1997), alcohol-induced aggressive behavior (Dougherty et al. 1999) or alcohol-related risk taking (Lane et al. 2004). Thus, female and male subjects were treated similarly, except that adjustments were made for alcohol dosing (see details below). All female subjects self-reported regular menstrual cycles over the past 6 months, with onset of menses every 27–31 days and had a negative pregnancy test, measured from urine samples collected each week of participation.

#### Point-subtraction aggression paradigm (PSAP)

The three-option PSAP is a computer-based task that pairs subjects with a fictitious counterpart (Cherek 1992). The subject repeatedly chooses between a monetary reinforced option, an aggressive option or an escape option. The PSAP has shown external validity as a measure of aggression (Moeller et al. 1998; Cherek and Lane 2001) and has been used in several dozen studies in the USA, Canada and Europe (Carre et al. 2009; Gerra et al. 2007).

Subjects were instructed to earn as much money as possible in the experimental session. Aggression was never mentioned; subjects were told that the purpose of the study was to see how mood and motor responding changed throughout the day following alcohol consumption and how its effects were moderated by zolmitriptan. Subjects participated by pressing buttons (labeled A, B and C) on a response panel that corresponded with letters on the computer monitor. Pushing the A button on the panel 100 consecutive times (fixed-ratio, FR 100), added 15 cents to the subject's counter. The B response, FR 10 presses, ostensibly subtracted 15 cents from the other person at no gain to the subject. The C response, FR 10 presses, protected the subject's money from being subtracted by the fictitious counterpart (provocation-free interval, or PFI, averaging 125 s). Subjects were provoked at random intervals throughout the session by having 15 cents subtracted from their counter; the subtraction was attributed to the fictitious counterpart.

Human aggression may be operationally defined as a social behavior that is intended to harm (present an aversive stimulus to) another person who finds this harm aversive and would act to avoid it (Baron and Richardson 1994). In accord with this operational definition, the rate of pressing button B was the primary measure of aggressive responding (B responses per provocation). Typically, aggressive (B) and escape (C) responding occurred shortly after one or more provocations. If the subject retaliated by aggressive responding, a temporary cessation of further provocations was initiated (PFI averaging 125 s). Aggressive responding was maintained (i.e., reinforced) in part by this cessation of further provocations. Subjects were not informed about this contingency,



only that pressing B subtracted 15 cents from the other person participating in the task. Subjects were informed, however, of the contingency that the C button produced a period of protection from provocations. Hence, the escape option served as a baseline condition against which to judge the specificity of button B responses as an aggressive response (Cherek et al. 2006). Subjects were ensured that no responses were required on the B option. The term aggression was not mentioned in the instructions.

The integrity of the social deception was evaluated using an open-ended questionnaire following the last experimental session of each day. Any report that indicated the participant did not believe the social deception, i.e., “I was not paired with anyone” or “I think it was a computer” resulted in the removal of the subject due to failure of the deception. All subjects' answers on the questionnaire were consistent with (a) the presence of other players and (b) were generally sensitive to their session earnings. For example, detectable decreases in earnings typically correlated with less favorable ratings of the other player. No subjects were removed from the present study based on the social deception.

### Study design

Subjects typically completed the study in 3 to 4 weeks, coming in 3 days a week; Monday, Wednesday, and Friday. Each day of the study, subjects arrived at approximately 8:00 a.m. Subjects completed 2 to 3 days of baseline testing on the PSAP to familiarize them with the task and stabilize their behavior prior to initiating dose administration. Once stability was established, dosing began. The study employed a within-subject design using counterbalanced dose sequences with intervening placebo doses. All six possible combinations (three alcohol doses  $\times$  two zolmitriptan doses) were used at least once. Due to subject time commitment (up to a month) and the within-subject design, the experiment included a relatively small number of subjects.

Subjects participated in five 25-minute experimental sessions each day. The first testing session began at 8:30 a.m., 15 min after administration of the capsule of zolmitriptan/placebo for that day. Following drink administration (alcohol/placebo) from 9:15–9:30 a.m., subjects completed four more test sessions at 10:00 a.m., 11:00 a.m. and 1:00 p.m., and 2:00 p.m. Five minutes prior to each test session, subjects completed a computerized version of the ARCI 49 (described below). Heart rate, blood pressure and BAL were measured upon arrival to the lab, immediately prior to alcohol dosing, 30 min after drink administration and immediately after each PSAP testing session. At 3:15, subjects were evaluated for signs of impairment or intoxication—first by a research assistant and

then by a study investigator. Impairment was determined by a standard field sobriety test. Following agreement by research assistant and investigator that the subject was unimpaired and verification of a BAL less than 0.02 ppm, the subject was released.

### Alcohol and zolmitriptan manipulation

At 8:15 a.m., a trained research assistant orally administered placebo or zolmitriptan doses (ZOMIG<sup>®</sup>, AstraZeneca, London, UK) in a small, unoccupied room. The contents of the capsules were blind to both the research assistant and the subject. Placebo doses were composed of one light blue, size 00 capsule filled with cornstarch. Active doses were composed of a 5-mg zolmitriptan tablet placed inside an identical capsule, also filled with cornstarch. A 5-mg dose was selected due to its safety profile, as per the manufacturer's suggested dose, and because this dose has shown safety and efficacy in human subjects in previous clinical pharmacology studies (Peterlin and Rapoport 2007). Subjects were required to show the capsule on their tongue before swallowing, and visual inspection aided by a tongue depressor was used to verify that the capsule has been swallowed. Alcohol was administered in a series of three cups of liquid totaling 24 oz.

Alcohol was 190 proof ethyl alcohol distilled by Gallipot<sup>®</sup> (St Paul, MN, USA). Drinks were mixed with 7-UP and a drop of peppermint extract to disguise the taste of alcohol. Three doses were tested: 0.0 g/kg (placebo), 0.4 g/kg or 0.8 g/kg. Neither the subject nor the research assistant was told the amount of alcohol in the drink. Regarding dose content, subjects were told in the informed consent document that, “During the study, you will be given alcohol and Zomig or a placebo. Placebo is a drink with no alcohol or a capsule with no Zomig... During all visits, you will be asked to drink a beverage. It will contain different amounts of alcohol mixed with 7-UP and peppermint added for flavoring. The amount of alcohol in each drink will vary from none (or placebo, which is no alcohol, just 7-UP and peppermint) to amounts that are meant to produce breath-alcohol levels (BAL) of 0.04 and 0.08.” Ethanol in milliliters was determined by conversion from kilograms based on body weight. For females, the amount of alcohol (mL) was multiplied by 0.85 to decrease the amount of alcohol they consumed relative to a male of equal weight and achieve equal blood alcohol concentrations across gender (Hindmarch et al. 1991; Lane et al. 2004).

Subjects were given the first cup of liquid at 9:15 a.m. and had 5 min to finish it, followed by the remaining two cups at 5-min intervals. The drink administration was completed by 9:30 a.m. All doses (including placebo) were prepared with a small amount of alcohol lining the rim of

the cup so that all drinks initially tasted and smelled of alcohol to maintain consistency across conditions. After finishing the dose at 9:30 a.m., subjects were given an additional 30 min for the alcohol to be absorbed, reach the central nervous system (CNS) and exert CNS effects. Onset of the effects of zolmitriptan occurs within 15 min and peaks at approximately 2 h (Uemura et al. 2005; Bergstrom et al. 2006). Alcohol's peak effects occur between 30 and 45 min (Harris et al. 2008). Thus, the dosing protocol was intended to simultaneously capture the peak effects of both drugs in sessions 2 (10:00 a.m.) and 3 (11:00 a.m.).

#### Subjective measures of drug effects

Subjective drug effects were measured by the Addiction Research Center Inventory (ARCI) short form (Martin et al. 1971). The ARCI short form is a 49-item true/false questionnaire that has been empirically derived to assess five different factors, including euphoria, sedation and dysphoria induced by a range of drug classes (Haertzen 1966; Martin et al. 1971). It is composed of five subscales designed to differentiate drug effects. The Pentobarbital–chlorpromazine–alcohol group (PCAG) is a subscale measuring sedation and intoxication, well-validated as an index of subjective effects in studies administering alcohol, barbiturates and benzodiazepines (Martin et al. 1971; Rush and Griffiths 1997; Zawertailo et al. 2003). No other subscales were sensitive to the dose conditions, and thus only the PCAG scale data are reported here. A computerized version was employed that required the subject to

move the mouse over the text presenting the question and then mouse click, which brought up the true/false response boxes. There was a 1-s delay between each answer and the presentation of the next question. This procedure served to prevent subjects from rapidly answering the items without attending to the questions—an outcome intermittently observed in our laboratory using paper and pencil versions of the ARCI 49.

#### Dependent measures

The primary dependent variable of interest was a ratio of the number of aggressive responses divided by the number of monetary-earning responses (aggressive/monetary or B/A). This ratio measure was used to account for shifts in behavior induced by both (a) potentiation of aggressive responding (button B) and (b) changes in motor output indexed by high-rate responding on the monetary-earning response option (button A). Because A responses account for >95% of all responding on the PSAP (see Table 1), this measure is roughly equivalent to the ratio of aggressive/total responses, an index used by previous investigators (McCloskey et al. 2009b).

Additional measures included the monetary (A) responses per second, escape (C) responses per minute, the subjective effects determined by the PCAG scale from the ARCI 49 questionnaire and physiological data: breath-alcohol concentration (BAC), heart rate and blood pressure. Blood pressure and heart rate data were collected to monitor safety, and BAC was measured to ensure accuracy

**Table 1** Means ( $\pm$ SEM) for aggressive, monetary and escape responding across all sessions and conditions. Note, only five of 11 subjects consistently used the escape option. One subject made approximately 400 responses per session across conditions

Response type	Session	0.0g/kg alcohol		0.4g/kg alcohol		0.8g/kg alcohol	
		Placebo	Zolmitriptan	Placebo	Zolmitriptan	Placebo	Zolmitriptan
Aggressive	1	162 $\pm$ 22	156 $\pm$ 24	163 $\pm$ 19	143 $\pm$ 19	155 $\pm$ 19	120 $\pm$ 19
	2	166 $\pm$ 29	154 $\pm$ 20	186 $\pm$ 34	127 $\pm$ 20	182 $\pm$ 38	152 $\pm$ 31
	3	158 $\pm$ 34	157 $\pm$ 24	191 $\pm$ 40	141 $\pm$ 25	179 $\pm$ 25	157 $\pm$ 30
	4	158 $\pm$ 24	166 $\pm$ 26	209 $\pm$ 48	167 $\pm$ 30	175 $\pm$ 17	167 $\pm$ 22
	5	165 $\pm$ 23	145 $\pm$ 23	204 $\pm$ 41	149 $\pm$ 19	200 $\pm$ 30	162 $\pm$ 34
Monetary	1	7196 $\pm$ 400	7188 $\pm$ 390	7383 $\pm$ 350	7111 $\pm$ 440	7365 $\pm$ 420	7115 $\pm$ 330
	2	7306 $\pm$ 430	7129 $\pm$ 420	7027 $\pm$ 400	6822 $\pm$ 470	6768 $\pm$ 480	6172 $\pm$ 660
	3	7240 $\pm$ 420	6948 $\pm$ 420	7219 $\pm$ 430	7057 $\pm$ 490	6470 $\pm$ 600	6070 $\pm$ 600
	4	7190 $\pm$ 430	7171 $\pm$ 410	7268 $\pm$ 430	7167 $\pm$ 440	6955 $\pm$ 430	6616 $\pm$ 360
	5	7248 $\pm$ 490	7233 $\pm$ 370	7192 $\pm$ 480	7163 $\pm$ 350	7218 $\pm$ 400	6897 $\pm$ 340
Escape responses	1	80.3 $\pm$ 30	87.3 $\pm$ 35	81.1 $\pm$ 31	75.1 $\pm$ 32	74.2 $\pm$ 33	74.6 $\pm$ 35
	2	76.8 $\pm$ 36	74.9 $\pm$ 31	124 $\pm$ 41	71.8 $\pm$ 28	67.3 $\pm$ 34	78.7 $\pm$ 42
	3	96.8 $\pm$ 61	79.7 $\pm$ 35	108 $\pm$ 40	57.9 $\pm$ 27	69.1 $\pm$ 35	80.0 $\pm$ 43
	4	90.5 $\pm$ 57	97.6 $\pm$ 40	135 $\pm$ 60	62.4 $\pm$ 24	69.1 $\pm$ 44	108 $\pm$ 55
	5	86.0 $\pm$ 39	80.1 $\pm$ 32	136 $\pm$ 56	68.2 $\pm$ 33	57.5 $\pm$ 30	108 $\pm$ 53

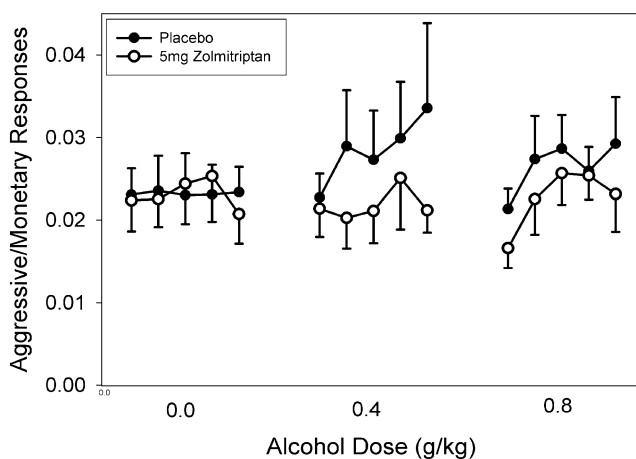
of alcohol doses. Supplemental measures (not reported here) included psychometric data collected after all dosing conditions were completed. Only five of 11 subjects consistently used the escape response option (mean  $157.38 \pm 18.07$  responses per session, see Table 1). Of these five, one subject averaged approximately 400 escape responses per session, highly skewing the average and the shape of the distribution. Accordingly, even after transformation, escape response data were not amenable to appropriate statistical analysis.

All statistical analyses were first conducted with gender as a factor. For the aggressive/monetary response ratio, there were no main effects of gender, nor were there any significant interactions among gender, alcohol, zolmitriptan and session. However, there was a trend toward a significant alcohol  $\times$  Zomig  $\times$  session  $\times$  gender interaction ( $p=0.062$ ). Similarly, for the PCAG (subjective effects) scale and BAC data, there were no main effects of gender and no interactions of gender with alcohol, Zomig or session. Subsequent analyses were conducted with gender removed from the ANOVA models.

## Results

### PSAP responding

The mean number of total monetary, aggressive and escape responses per session across all sessions and conditions is provided in Table 1. Figure 1 shows the mean aggressive/monetary response ratio for each session across each dose condition. An ANOVA on the aggressive/monetary ratio with repeated measures on alcohol dose, zolmitriptan dose



**Fig. 1** Ratio of number of aggressive/monetary responses (*Y* axis) across each of the five daily test sessions and each of the alcohol dosing conditions (*X* axis). Each data point shows the mean ( $\pm$ SEM) for the 11 subjects. Black circles show 0-mg zolmitriptan (placebo) and open circles show 5-mg zolmitriptan doses

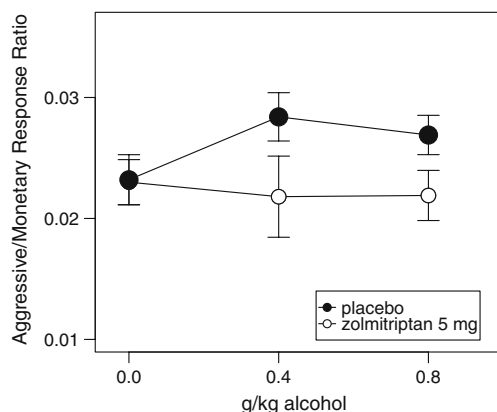
and session revealed a statistically significant main effect of session [ $F(4, 40)=3.22$ ,  $p=0.035$  with Huynh–Feldt correction] and a significant alcohol  $\times$  zolmitriptan interaction [ $F(2, 20)=3.14$ ,  $p=0.045$  with Huynh–Feldt correction]. For the interaction, Tukey HSD follow-up tests ( $\alpha=0.05$ ) showed that the aggressive/monetary response ratio was significantly lower under 5-mg zolmitriptan vs. 0-mg zolmitriptan at both the 0.4-g/kg and 0.8-g/kg alcohol doses, suggesting that zolmitriptan diminished aggressive responding at those alcohol doses. A summary of the alcohol–zolmitriptan interaction is provided graphically in Fig. 2, which presents aggressive/monetary response ratios averaged across the five experimental sessions for each alcohol–zolmitriptan dose combination. There was not a main effect of alcohol, while there was a trend towards a main effects of zolmitriptan [ $F(1, 10)=4.17$ ,  $p=0.068$  with Huynh–Feldt correction]. The alcohol  $\times$  zolmitriptan  $\times$  session interaction was not significant ( $F < 1$ ).

### Subjective effects

The subjective effects measured by the PCAG scale of the showed a significant main of session, ( $F(4, 40)=3.38$ ,  $p=0.014$ ), suggesting that, across conditions, mood changed throughout the day. Tukey HSD follow-up tests showed that PCAG scores were significantly higher in session 3 vs. session 1. There was a trend toward a main effect of alcohol [ $F(2, 20)=3.30$ ,  $p=0.058$ ]. There was not a main effect of zolmitriptan on the PCAG subscale scores ( $F < 1$ ), and there were no significant interactions among alcohol, zolmitriptan and session.

### Breath-alcohol concentration (BAC)

BAC readings obtained across each experimental day revealed that alcohol concentrations were slightly lower than the intended levels of 0.04 and 0.08, corresponding with 0.4-g/kg and 0.8-g/kg alcohol doses. Peak BAC occurred 0.5 h (session 2) after alcohol administration for three doses, 0.4 g/kg with zolmitriptan ( $M=0.034 \pm 0.003$ ) and placebo capsules ( $M=0.034 \pm 0.003$ ) and 0.8 g/kg with placebo capsules ( $M=0.065 \pm 0.008$ ). The peak BAC for the 0.8-g/kg dose with zolmitriptan capsules occurred 1 h after alcohol administration ( $M=0.065 \pm 0.005$ ), measured just after subjects finished session 2. Hence, alcohol concentrations were at their peak during the second session of the day, between 10:00 and 11:00 a.m. BAC was analyzed using three-way repeated-measures ANOVA for session, alcohol and zolmitriptan. Not surprisingly, there was a significant main effect of alcohol [ $F(2, 20)=100.88$ ,  $p < 0.001$ ; 0.8 significantly  $> 0.04$  g/kg]. Interestingly, there was also a significant alcohol  $\times$  Zomig  $\times$  session interaction [ $F(4, 40)=3.58$ ,  $p=0.014$ ]. Tukey HSD follow-up tests



**Fig. 2** Summary of the ratio of number of aggressive/monetary responses (*Y* axis) averaged over five daily test sessions (mean of Fig. 1) across each of the alcohol dosing conditions (*X* axis). Each data point shows the mean ( $\pm$ SEM) for the 11 subjects. Black circles show 0-mg zolmitriptan (placebo) and open circles show 5-mg zolmitriptan doses. The figure summarizes graphically the significant alcohol  $\times$  Zomig interaction revealed in repeated-measures ANOVA. See text for details

revealed the following outcomes: (a) at the 0.4-g/kg alcohol dose, BAC was significantly higher for 5-mg vs. 0-mg zolmitriptan following session 3, approximately 2 h post-alcohol dose; and (b) at the 0.8-g/kg alcohol dose, BAC was significantly higher for 5-mg vs. 0-mg zolmitriptan following sessions 3 and 4, from 2–4 h post-dose.

## Discussion

The primary purpose of this study was to determine whether the 5-HT<sub>1B/D</sub> agonist zolmitriptan could attenuate alcohol-heightened aggression in human subjects. The data indicated an interaction between zolmitriptan and alcohol, where zolmitriptan selectively decreased aggressive responding on the PSAP relative to monetary responding at both active alcohol doses (0.04 and 0.08 g/kg). This interaction suggests a relationship (albeit complex) between alcohol-heightened aggression and the 5-HT system. In particular, human 5-HT<sub>1B/D</sub> receptors may partially mediate the relationship between 5-HT and alcohol. As suggested by de Almeida et al. (2006), zolmitriptan may decrease aggressive behavior by augmenting serotonergic function in the OFC, a region putatively involved in inhibitory control of aggressive behavior (New et al. 2004). Thus, these receptors are a potentially rich target for anti-aggressive pharmacological intervention. Below we discuss implications and limitations of the present data.

Attempts to acutely manipulate serotonin function concurrently with alcohol dosing in humans have been limited to a few studies. In one study, acute tryptophan

depletion and concurrent alcohol dosing produced increases in aggression, whereas tryptophan loading decreased aggression; however, the tryptophan effects were independent of alcohol effects on aggression (Pihl et al. 1995). More recent work examining the effects of alcohol and paroxetine on human aggression found main effects for paroxetine in reducing aggression and for alcohol in increasing aggression (McCloskey et al. 2009a, b). Notably, and in contrast to the present findings, neither of these previous studies found a significant alcohol  $\times$  serotonin interaction.

Three possible factors may explain the differences in our results and these previous studies. First, both Pihl et al. (1995) and McCloskey et al. (2009a, b) used pharmacological agents that modify the 5-HT system in a non-specific fashion, via precursor loading/depletion or blockade of 5-HT reuptake. In contrast, zolmitriptan is a direct agonist at the 5-HT<sub>1B/D</sub> receptor and, as demonstrated preclinically by de Almeida et al. (2001, 2006), its pharmacological specificity at these receptor sites may be important in diminishing alcohol-related aggression. Second, differences in methodological design and the aggression measures utilized may have contributed to different outcomes. Specifically, previous studies tested at a single time point related to peak pharmacological effects, whereas the present study used a repeated-measures design with testing at five time points spread over a 5.5-h period. While this design strategy has limitations (e.g., higher drop out and small sample sizes), it may enhance the ability to detect pharmacological effects by increasing both the number of duration of testing opportunities. Third, the ability of the PSAP to be given repeatedly allows for such repeated measure designs, in contrast to the TAP used in both Pihl et al. (1995) and McCloskey (2009a, b) studies, which can generally be presented to subjects only once. However, the PSAP also measures a different dimension of aggressive behavior (frequency) than the TAP (intensity). Thus, the present findings may be relevant only to this characteristic of aggressive behavior. In light of these procedural and measurement differences, the role of serotonin modulation in alcohol-related aggression is in need of further examination. Additionally, the discrepant research findings leave unclear results whether alcohol interacts directly or indirectly with the endogenous serotonin system in altering the propensity for human aggression.

In support of our findings with human subjects, studies employing mouse models have demonstrated the utility of modulating serotonin via the 5-HT<sub>1B/D</sub> receptor to decrease alcohol-induced aggression (Fish et al. 1999; de Almeida et al. 2001). Although the mouse 5-HT<sub>1B/D</sub> receptors are not direct homologues of the human 5-HT<sub>1B/D</sub> receptor subtypes (Olivier and van Oorschot 2005), the present study indicates the potential similarity of its anti-aggressive



effects. Further, as there remain few available serotonergic agents that have demonstrated therapeutic potential for managing aggression, 5-HT<sub>1B/D</sub> agonists merit consideration in future human research.

More than any other substance, studies have demonstrated that alcohol can increase aggression and violence in a portion of individuals (Taylor et al. 1976; Cherek et al. 1985; Martin and Bryant 2001; Giancola et al. 2003; review by Bushman 1997). Elucidating the biological mechanism by which alcohol causes this change remains an important question. Until recently, it was unclear whether or not alcohol produced its behavioral effects through modulation of neurotransmitter systems like most psychopharmacologic agents or indirectly through an unknown mechanism, but recent research has indicated that a sub-type of the GABA-A receptor displays enhanced sensitivity at low alcohol concentrations (3 mM) which approximate social drinking (Hancher et al. 2004). One possibility is that GABAergic neurons may impinge on the 5-HT system to alter aggression, suggesting an indirect 5-HT alcohol relationship in aggression.

The literature also suggests a possible sequence of events which give rise to a more direct relationship with 5-HT in alcohol-induced aggression. It has been demonstrated that low levels of serotonin are associated with increased aggressive behavior (Brown et al. 1979; Miczek et al. 2002) and that the administration of alcohol gives rise to aggressive behavior (Bushman 1997; Taylor 1976; Giancola et al. 2003). Additionally, alcoholics have lower serotonin levels (Ballenger et al. 1979), raising serotonin levels can curb alcohol intake (Sellers et al. 1992), and alcohol can decrease serotonin release and binding affinity (Akash et al. 2008). Therefore, augmenting serotonin function concurrently with the administration of alcohol may diminish some of the aggression-heightening effects of alcohol. As noted, alcohol might heighten aggression, in part, by decreasing serotonergic function (Faccidomo et al. 2008). This could create a cyclical situation, where drinking alcohol decreases serotonin function, and decreased serotonin levels promote both higher levels of aggression and further alcohol consumption. However, as previous studies did not find an interaction between alcohol and serotonin modulation through either tryptophan manipulation or paroxetine administration (Pihl et al. 1995; McCloskey et al. 2009a, b), it remains possible that serotonin modifies aggression through a pathway that is indirectly related to alcohol effects. The present results raise the possibility that the 5-HT<sub>1B/D</sub> receptor may play a role in mediating this relationship in humans, but future studies will be needed to inform the precise nature of this interaction.

The repeated-measures experimental design and the nature of the PSAP task necessarily limit the sample size to a relatively small number ( $N=11$ ). This limitation

constrains the generalizability of the findings. Further, the relatively low levels of alcohol employed in this study (BAC in the 0.035 to 0.065 range) may not approximate the levels of intoxication involved in violence in natural settings. It is unknown how prevalent this effect would be in a broader population, a sample of subjects with a history of alcohol-related violence, or a sample comprised of only individuals with a history of alcohol abuse and dependence. One strategy for future work may be the selection of a sample with a history of trait aggression which may enhance the results as previous studies have shown that high trait aggression is a predictor of alcohol-related aggressive behavior (Miller et al. 2009).

The PSAP is a measure of reactive aggression; subjects engage in responding on the aggressive option in reaction to provocation. It is unknown if zolmitriptan could diminish other forms of alcohol-related aggressive behavior, such as proactive (goal directed) aggression, or mitigate factors known to be related to aggression such as stress, frustration and more general problems of impulse control. Both alcohol administration and poor serotonin function have been indicated in impulsivity (Fillmore 2003; Moeller et al. 2001), and zolmitriptan's effects on impulse control deserve further attention. This could help delineate aggression-specific effects from those related to general changes in impulse control. As noted above, the PSAP measures one dimension of aggressive responding (frequency), while other laboratory tasks measure other dimensions such as intensity of physical aggression (McCloskey and Berman 2003; Taylor 1976; Parrott and Giacola 2007). It is not clear that these results would generalize to such dimensions. Due to the small sample size, the generality of the results must also be considered with caution. These limitations should be addressed in future studies that more broadly examine aggressive and impulsive behaviors.

A previous study using paroxetine administration found reductions in impulsivity concurrent with reductions in aggression (Cherek et al. 2002). Thus, while we only observed a trend for a main effect of zolmitriptan on aggression, it could potentially be effective for reducing non-alcohol induced reactive aggression in individuals at high risk for aggressive behavior. However, more supportive data will be needed to clarify the direct effects of zolmitriptan on aggression. We did not observe gender differences in this study. Our sample was limited to four females and thus was not sufficient to detect interactions with gender. Given well-established gender differences in alcohol effects on aggression (Dougherty et al. 1996; Giancola et al. 2009), this is a notable limitation in the current findings. The role of gender and the menstrual cycle deserve greater attention as potential factors in the alcohol-serotonin relationship. Though often treated separately from males, female serotonin function exhibits a similar inverse

relationship with aggressive behavior (Bond et al. 2001). Elevated estradiol levels, which occur during the middle-phase of the menstrual cycle, are associated with increases in aggressive behavior and, to a lesser extent, with increases on non-aggressive risk taking (Vermeersch et al. 2008). Future work should control for phase of the menstrual cycle or investigate zolmitriptan's interaction with heightened-aggression resulting from hormonal changes and alcohol effects.

Despite the limitations, this study presents preliminary evidence in humans that 5-HT function, particularly the 5-HT<sub>1B/D</sub> receptor, may play a key role in regulating alcohol-heightened aggression. More broadly, zolmitriptan and other triptan drugs hold promise as challenge or intervention agents as a means for modifying human aggressive behavior.

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